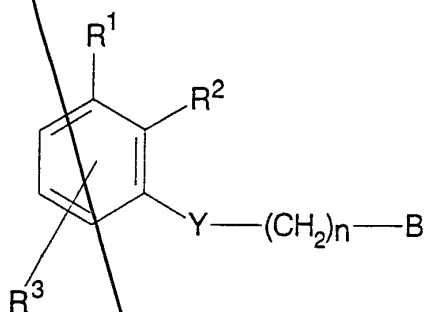


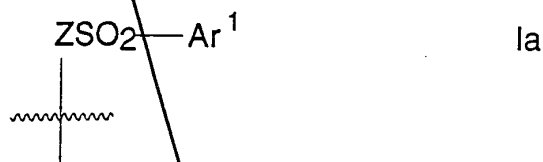
## Claims

1. A compound of formula I,



wherein

one of  $R^1$  and  $R^2$  represents a structural fragment of formula Ia



and the other represents  $R^4$ ;

$Z$  represents O or  $N(R^5)$ ;

$R^3$  represents one or more optional substituents selected from OH, halo, cyano, nitro,  $C(O)OR^6$ ,  $C_{1-6}$  alkoxy or  $C_{1-6}$  alkyl (which two latter groups are optionally substituted and/or terminated by one or more halo or hydroxy group) or  $N(R^7)R^8$ ;

$R^4$  represents H, OH, halo, cyano, nitro,  $C(O)OR^6$ ,  $C_{1-6}$  alkoxy or  $C_{1-6}$  alkyl (which two latter groups are optionally substituted and/or terminated by one or more halo or hydroxy group) or  $N(R^7)R^8$ ;

$Ar^1$  represents phenyl,  $C_{1-3}$  alkylphenyl,  $C_{1-3}$  alkylidiphenyl,  $C_{3-7}$  cycloalkyl,  $C_{1-3}$ -alkyl- $C_{3-7}$ -cycloalkyl,  $C_{1-3}$ -alkyl-di- $C_{3-7}$ -cycloalkyl, naphthyl,  $C_{1-3}$  alkyl naphthyl, thienyl, imidazolyl or isoxazolyl, all of which may be substituted by one or more substituent selected from OH, halo, cyano, nitro,  $C(O)OR^6$ ,  $C_{1-6}$  alkoxy or  $C_{1-6}$  alkyl (which two latter groups are optionally

substituted and/or terminated by one or more halo or hydroxy group) or  $N(R^7)R^8$ ;

$R^5$  represents H,  $C_{1-6}$  alkyl, phenyl or  $C_{1-3}$  alkylphenyl (which three latter groups are optionally substituted and/or terminated by one or more substituent selected from OH, halo, cyano, nitro,  $C(O)OR^9$ ,  $C(O)N(R^{10})R^{11}$ ,  $P(O)(R^{12})R^{13}$ ,  $P(O)(OR^{14})OR^{15}$ ,  $S(O)_2(R^{16})R^{17}$ ,  $S(O)_2N(R^{18})R^{19}$ ,  $C_{1-6}$  alkoxy or  $C_{1-6}$  alkyl (which two latter groups are optionally substituted and/or terminated by one or more halo or hydroxy group) or  $N(R^{20})R^{21}$ );

Y represents O, S,  $S(O)$ ,  $S(O)_2$  or  $N(R^{22})$ ;

$R^{10}$  and  $R^{11}$  independently represent H,  $OR^{23}$ ,  $C(O)R^{24}$ ,  $OC(O)R^{25}$ ,  $C(O)OR^{26}$ ,  $C_{1-4}$  alkyl, (which latter group is optionally substituted and/or terminated by one or more substituent selected from  $C_{1-4}$  alkyl,  $OR^{27}$ ,  $N(R^{28})R^{29}$ ,  $C(O)OR^{30}$ ,  $C(O)N(R^{31})R^{32}$ ,  $P(O)(R^{33})R^{34}$ ,  $P(O)(OR^{35})OR^{36}$  and  $S(O)_2N(R^{37})R^{38}$ ),  $-(CH_2CH_2O)_pR^{39}$  or, together with the nitrogen atom to which they are attached, form a  $C_{4-7}$  nitrogen-containing, aromatic or non-aromatic, ring which ring may contain a further heteroatom or group (as appropriate) selected from O, S and  $N(R^{40})$  and may further be substituted by one or more substituent selected from  $C(O)R^{41}$ ,  $C(O)OR^{42}$  or  $C(O)N(R^{43})R^{44}$ ;

$R^{28}$ ,  $R^{29}$ ,  $R^{30}$ ,  $R^{31}$ ,  $R^{32}$  and  $R^{40}$  independently represent H or  $C_{1-6}$  alkyl, which latter group is optionally substituted and/or terminated by one or more substituent selected from  $C(O)R^{45}$ ,  $C(O)OR^{46}$  or  $C(O)N(R^{47})R^{48}$ ;

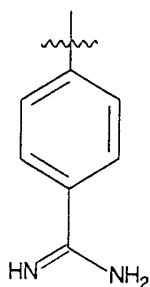
at each occurrence,  $R^6$ ,  $R^7$  and  $R^8$  independently represent H or  $C_{1-4}$  alkyl;  $R^9$ ,  $R^{12}$ ,  $R^{13}$ ,  $R^{14}$ ,  $R^{15}$ ,  $R^{16}$ ,  $R^{17}$ ,  $R^{18}$ ,  $R^{19}$ ,  $R^{20}$ ,  $R^{21}$ ,  $R^{22}$ ,  $R^{23}$ ,  $R^{24}$ ,  $R^{25}$ ,  $R^{26}$ ,  $R^{27}$ ,  $R^{33}$ ,  $R^{34}$ ,  $R^{35}$ ,  $R^{36}$ ,  $R^{37}$ ,  $R^{38}$ ,  $R^{39}$ ,  $R^{41}$ ,  $R^{42}$ ,  $R^{43}$ ,  $R^{44}$ ,  $R^{45}$ ,  $R^{46}$ ,  $R^{47}$  and  $R^{48}$  independently represent H or  $C_{1-4}$  alkyl;

n represents 0, 1, 2, 3 or 4;

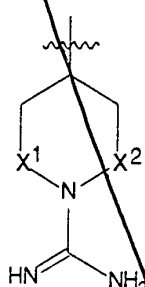
p represents 1, 2, 3, 4, 5 or 6; and

B represents a structural fragment of formula Ib, Ic, Id or Ie

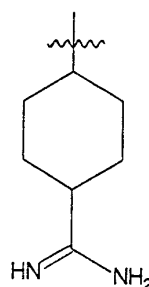
Cont.



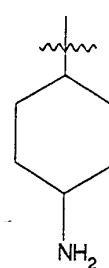
Ib



Ic



Id



Ie

wherein

$X^1$  and  $X^2$  independently represent a single bond or  $CH_2$ ;  
or a pharmaceutically acceptable salt thereof.

2. A compound of formula I, as defined in Claim 1, wherein, when B represents a structural fragment of formula Ib, Id, Ie or Ic in which latter fragment  $X^1$  and  $X^2$  both represent  $CH_2$ , then n represents 2.

3. A compound of formula I, as defined in one Claim 1, wherein n represents 2.

4. A compound of formula I, as defined in any one of the preceding claims, wherein  $R^2$  represents a structural fragment of formula Ia and  $R^1$  represents  $R^4$ .

15

5. A compound of formula I, as defined in any one of the preceding claims, wherein Z represents O or  $N(R^5)$ , in which latter case  $R^5$  represents  $C_{1-6}$  alkyl terminated by  $C(O)N(R^{10})R^{11}$ .

6. A compound of formula I, as defined in any one of the preceding claims, wherein  $R^3$  is not present, or represents methyl, chloro or methoxy.

7. A compound of formula I, as defined in any one of the preceding claims, wherein Ar<sup>1</sup> represents substituted phenyl.
8. A compound of formula I, as defined in any one of the preceding claims wherein Y represents O.
9. A compound of formula I, as defined in any one of the preceding claims wherein B represents a structural fragment of formula Ib.
10. A compound as claimed in Claim 1 which is:
- N-{3-[2-(4-aminoiminomethylphenyl)ethoxy]phenyl}benzenesulfonamide;  
benzenesulfonic acid-{3-[2-(4-aminoiminomethylphenyl)ethoxy]-5-methyl}phenyl ester;  
N-{3-[2-(4-aminoiminomethylphenyl)ethoxy]phenyl}-2-chlorobenzenesulfonamide;  
N-{3-[2-(4-aminoiminomethylphenyl)ethoxy]phenyl}-2-cyanobenzene-sulfonamide;  
N-{3-[2-(4-aminoiminomethylphenyl)ethoxy]phenyl}-2-fluorobenzene-sulfonamide;  
N-{3-[2-(4-aminoiminomethylphenyl)ethoxy]phenyl}-2-(trifluoromethoxy)-benzenesulfonamide;  
N-{3-[2-(4-aminoiminomethylphenyl)ethoxy]phenyl}-4-fluorobenzene-sulfonamide;  
N-{3-[2-(4-aminoiminomethylphenyl)ethoxy]phenyl}-2,5-dimethylbenzene-sulfonamide;  
N-{3-[2-(4-aminoiminomethylphenyl)ethoxy]phenyl}-5-chlorothiophene-2-sulfonamide;  
N-{3-[2-(4-aminoiminomethylphenyl)ethoxy]phenyl}-1-methylimidazole-3-sulfonamide;  
N-{3-[2-(4-aminoiminomethylphenyl)ethoxy]phenyl}-3,5-dimethylisoxazole-

30 3-{3-[2-(4-aminoiminomethylphenyl)ethoxy]-N-(2-chlorophenyl)sulfonyl-5-

- methylphenylamino} butanamide;
- N-(2-chlorophenyl)sulfonyl-3-{3-[2-(4-aminoiminomethylphenyl)ethoxy]-5-methylphenylamino} butanoic acid;
- N-(2-chlorophenyl)sulfonyl-4-{3-[2-(4-aminoiminomethylphenyl)ethoxy]-5-methylphenylamino} pentanoic acid, ethyl ester;
- 4-{3-[2-(4-aminoiminomethylphenyl)ethoxy]-N-(2-chlorophenyl)sulfonyl-5-methylphenylamino} pentanamide;
- N-(2-chlorophenyl)sulfonyl-4-{3-[2-(4-aminoiminomethylphenyl)ethoxy]-5-methylphenylamino} pentanoic acid;
- 10 N-(2-chlorophenyl)sulfonyl-5-{3-[2-(4-aminoiminomethylphenyl)ethoxy]-5-methylphenylamino} hexanoic acid, ethyl ester;
- 5-{3-[2-(4-aminoiminomethylphenyl)ethoxy]-N-(2-chlorophenyl)sulfonyl-5-methylphenylamino} pentanamide;
- N-(2-chlorophenyl)sulfonyl-5-{3-[2-(4-aminoiminomethylphenyl)ethoxy]-5-methylphenylamino} hexanoic acid;
- 15 N-phenylsulfonyl-3-[2-(4-aminoiminomethylphenyl)ethoxy]phenylaminoacetic acid, ethyl ester;
- N-phenylsulfonyl-3-[2-(4-aminoiminomethylphenyl)ethoxy]phenylaminoacetic acid;
- 20 N-{3-[2-(4-aminoiminomethylphenyl)ethoxy]phenyl}-N-(2-hydroxyethyl)-benzenesulfonamide;
- N-{3-[2-(4-aminoiminomethylphenyl)ethoxy]phenyl}-N-(dimethyloxophosphinylmethyl)-benzenesulfonamide;
- 2-chlorobenzenesulfonic acid, 3-[2-(4-aminoiminomethylphenyl)ethoxy]-5-methylphenyl ester;
- 25 benzenesulfonic acid, 3-[2-(4-aminoiminomethylphenyl)ethoxy]phenyl ester;
- 2-chloro-4-fluorobenzenesulfonic acid, 3-[2-(4-aminoiminomethylphenyl)ethoxy]-5-chlorophenyl ester;
- 2-chlorobenzenesulfonic acid, 3-[2-(4-aminoiminomethylphenyl)ethoxy]-5-methoxyphenyl ester;
- 30

- 2-chlorobenzenesulfonic acid, 3-[2-(4-aminoiminomethylphenyl)ethoxy]-5-ethylphenyl ester;
- N-{2-[2-(4-aminoiminomethylphenyl)ethylthio]phenyl} benzenesulfonamide;
- N-{2-[2-(4-aminoiminomethylphenyl)ethylthio]phenyl}-2,4,5-trichloro-
- 5 benzenesulfonamide;
- N-{2-[2-(4-aminoiminomethylphenyl)ethylthio]phenyl}-2-chloro-5-methoxybenzenesulfonamide;
- N-{2-[2-(4-aminoiminomethylphenyl)ethylthio]phenyl}-2,5-dibromobenzenesulfonamide;
- 10 N-{2-[2-(4-aminoiminomethylphenyl)ethylthio]phenyl}-2,5-dichlorobenzenesulfonamide;
- N-{2-[2-(4-aminoiminomethylphenyl)-ethylthio]-phenyl}-2-methoxy-5-methylbenzenesulfonamide;
- N-{2-[2-(4-aminoiminomethylphenyl)ethylthio]phenyl}-2,3,5,6-
- 15 tetramethylbenzenesulfonamide;
- N-{2-[2-(4-aminoiminomethylphenyl)ethylthio]phenyl}-3,4-dimethoxybenzenesulfonamide;
- N-{2-[2-(4-aminoiminomethylphenyl)ethylthio]phenyl}-3-bromobenzenesulfonamide;
- 20 N-{2-[2-(4-aminoiminomethylphenyl)ethylthio]phenyl}-3,4-dibromobenzenesulfonamide;
- N-{2-[2-(4-aminoiminomethylphenyl)ethylthio]phenyl}-2-chloro-4-fluorobenzenesulfonamide; or
- N-{2-[2-(4-aminoiminomethylphenyl)ethylthio]phenyl}-5-bromo-2-
- 25 methoxybenzenesulfonamide.

11. A compound of formula I, as defined in Claim 1, provided that R<sup>1</sup> represents a structural fragment of formula Ia and R<sup>2</sup> represents R<sup>4</sup>.

30 12. A compound of formula I, as defined in Claim 1, provided that Ar<sup>1</sup>

represents optionally substituted phenyl.

13. A compound of formula I, as defined in Claim 1, provided that  $R^5$  is not substituted by  $P(O)(OR^{14})OR^{15}$ ,  $S(O)_2(R^{16})R^{17}$  or  $S(O)_2N(R^{18})R^{19}$ .

5

14. A compound of formula I, as defined in Claim 1, provided that  $R^{10}$  and/or  $R^{11}$  represent H or unsubstituted  $C_{1-4}$  alkyl.

15. A compound of formula I, as defined in Claim 1, provided that Y  
10 represents O, S or  $N(R^5)$ .

16. A compound of formula I, as defined in Claim 1, provided that B represents a structural fragment of formula Ib, Ic or Id.

17. A compound of formula I, as defined in Claim 1, provided that  $R^2$   
15 represents a structural fragment of formula Ia and  $R^1$  represents  $R^4$ .

18. A compound of formula I, as defined in Claim 1, provided that  $Ar^1$  does not represent optionally substituted phenyl.

20

19. A compound of formula I, as defined in Claim 1, provided that  $R^5$  is substituted by  $P(O)(OR^{14})OR^{15}$ ,  $S(O)_2(R^{16})R^{17}$  or  $S(O)_2N(R^{18})R^{19}$ .

20. A compound of formula I, as defined in Claim 1, provided that  $R^{10}$   
25 and/or  $R^{11}$  do not represent H or unsubstituted  $C_{1-4}$  alkyl.

21. A compound of formula I, as defined in Claim 1, provided that Y represents  $S(O)$  or  $S(O)_2$ .

30 22. A compound of formula I, as defined in Claim 1, provided that B

T00000-6096E860



represents a structural fragment of formula Ie.

23. A pharmaceutical formulation including a compound as defined in any one of Claims 1 to 22, or a pharmaceutically acceptable salt thereof, in admixture with a pharmaceutically acceptable adjuvant, diluent or carrier.

24. A compound as defined in any one of Claims 1 to 22, or a pharmaceutically acceptable salt thereof, for use as a pharmaceutical.

25. A compound as defined in any one of Claims 1 to 22, or a pharmaceutically acceptable salt thereof, for use in the treatment of a condition where inhibition of thrombin is required.

26. A compound as defined in any one of Claims 1 to 22, or a pharmaceutically acceptable salt thereof, for use in the treatment of thrombosis.

27. A compound of formula I as defined in any one of Claims 1 to 22, or a pharmaceutically acceptable salt thereof, for use as an anticoagulant.

28. The use of a compound I as defined in any one of Claims 1 to 22, or a pharmaceutically acceptable salt thereof as active ingredient in the manufacture of a medicament for the treatment of a condition where inhibition of thrombin is required.

29. The use as claimed in Claim 28, wherein the condition is thrombosis.

30. The use of a compound defined in any one of Claims 1 to 22, or a pharmaceutically acceptable salt thereof, as active ingredient in the manufacture of an anticoagulant.

Sec A.

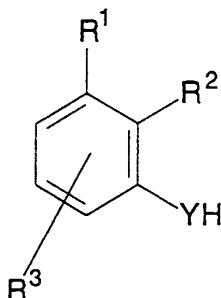
31. A method of treatment of a condition where inhibition of thrombin is required which method comprises administration of a therapeutically effective amount of a compound as defined in any one of Claims 1 to 22, or a pharmaceutically acceptable salt thereof, to a person suffering from, or susceptible to, such a condition.

32. A method as claimed in Claim 31, wherein the condition is thrombosis.

33. A method as claimed in Claim 31, wherein the condition is hypercoagulability in blood and tissues.

34. A process for the preparation of compounds of formula I which comprises:

(a) reaction of a compound of formula II,



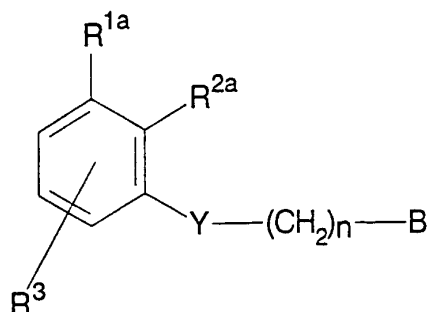
II

wherein R<sup>1</sup>, R<sup>2</sup>, R<sup>3</sup> and Y are as defined in Claim 1 with a compound of formula III,



wherein L<sup>1</sup> represents a suitable leaving group and n and B are as defined in Claim 1;

(b) reaction of a compound of formula IV,



IV

wherein one of  $R^{1a}$  and  $R^{2a}$  represents ZH and the other represents  $R^4$ , and Z,  $R^3$ ,  $R^4$ , Y, n and B are as defined in Claim 1 with a compound of formula

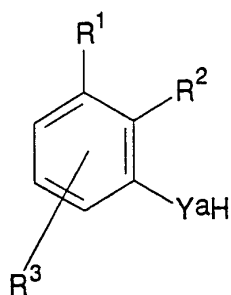
10 V,



wherein  $L^2$  is a suitable leaving group and  $Ar^1$  is as defined in Claim 1;

(c) for compounds of formula I in which Y represents O or S, reaction of a compound of formula VI,

15



VI

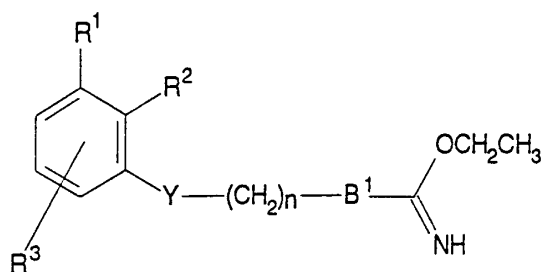
20

wherein  $Y^a$  represents O or S and  $R^1$ ,  $R^2$  and  $R^3$  are as defined in Claim 1 with a compound of formula VII,



25 wherein n and B are as defined in Claim 1;

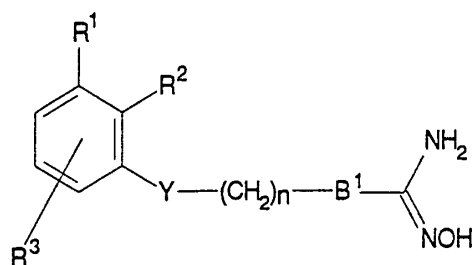
(d) for compounds of formula I wherein B represents a structural fragment of formula Ib or Id, reaction of a compound of formula VIII,



VIII

wherein B<sup>1</sup> represents 1,4-phenylene or 1,4-cyclohexylene and R<sup>1</sup>, R<sup>2</sup>, R<sup>3</sup>, Y and n are as defined in Claim 1 with ammonia gas;

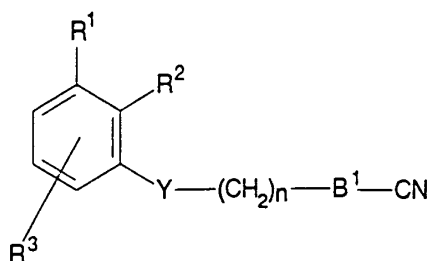
(e) for compounds of formula I wherein B represents a structural fragment of formula Ib or Id, reduction of a compound of formula IX,



IX

wherein R<sup>1</sup>, R<sup>2</sup>, R<sup>3</sup>, Y and n are as defined in Claim 1 and B<sup>1</sup> is as defined above;

(f) for compounds of formula I wherein B represents a structural fragment of formula Ib or Id, reaction of a compound of formula X,

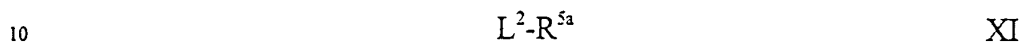


X

wherein  $R^1$ ,  $R^2$ ,  $R^3$ ,  $Y$  and  $n$  are as defined in Claim 1 and  $B^1$  is as defined above;

(g) for compounds of formula I wherein  $Y$  represents  $S(O)$  or  $S(O)_2$ , oxidation of a corresponding compound of formula I wherein  $Y$  represents  
 5  $S$ ;

(h) for compounds of formula I wherein  $Z$  represents  $N(R^5)$  and  $R^5$  represents optionally substituted  $C_{1-6}$  alkyl, phenyl or  $C_{1-3}$  alkylphenyl, reaction of a corresponding compound of formula I wherein  $Z$  represents  $NH$  with a compound of formula XI,



wherein  $R^{5a}$  represents optionally substituted  $C_{1-6}$  alkyl, phenyl or  $C_{1-3}$  alkylphenyl and  $L^2$  is as defined above;

(i) for compounds of formula I wherein  $Z$  represents  $N(R^5)$  and  $R^5$  represents  $C_{1-6}$  alkyl, phenyl or  $C_{1-3}$  alkylphenyl, all of which are substituted and/or  
 15 terminated by  $C(O)N(R^{10})R^{11}$ , reaction of a corresponding compound of formula I wherein  $R^5$  represents  $C_{1-6}$  alkyl, phenyl or  $C_{1-3}$  alkylphenyl, all of which are substituted and/or terminated, by  $C(O)OR^9$ , and  $R^9$  is as defined in Claim 1, with a compound of formula XII,



20 wherein  $R^{10}$  and  $R^{11}$  are as defined in Claim 1;

(j) for compounds of formula I wherein  $Z$  represents  $N(R^5)$  and  $R^5$  represents  $C_{1-6}$  alkyl, phenyl or  $C_{1-3}$  alkylphenyl, all of which are substituted and/or terminated by  $C(O)OH$ , hydrolysis of a corresponding compound of formula I wherein  $R^5$  represents  $C_{1-6}$  alkyl, phenyl or  $C_{1-3}$  alkylphenyl, all of which  
 25 are substituted and/or terminated by  $C(O)OR^9$  and  $R^9$  represents  $C_{1-4}$  alkyl;  
 or

(k) for compounds of formula I wherein  $Z$  represents  $N(R^5)$  and  $R^5$  represents  $(CH_2)_2C(O)OR^9$  and  $R^9$  is as defined in Claim 1, reaction of a corresponding compound of formula I wherein  $R^5$  represents  $H$  with a  
 30 compound of formula XIII,



wherein  $R^9$  is as defined in Claim 1.